DOCKET NO.: 279556US0PCT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: Fumie TAKAHASHI, et al.
SERIAL NO.: NEW U.S. PCT APPLICATION
FILED: HEREWITH
INTERNATIONAL APPLICATION NO.: PCT/JP04/05987
INTERNATIONAL FILING DATE: April 26, 2004
FOR: 1,2-DIARYLIMIDAZOLES USEFUL AS INHIBITORS OF COX

REQUEST FOR PRIORITY UNDER 35 U.S.C. 119 AND THE INTERNATIONAL CONVENTION

Commissioner for Patents
Alexandria, Virginia 22313

Sir:

In the matter of the above-identified application for patent, notice is hereby given that the applicant claims as priority:

COUNTRY	APPLICATION NO	DAY/MONTH/YEAR
Australia	2003902208	08 May 2003
Australia	2003903861	24 July 2003
Australia	2003904068	01 August 2003

Certified copies of the corresponding Convention application(s) were submitted to the International Bureau in PCT Application No. PCT/JP04/05987. Receipt of the certified copy(s) by the International Bureau in a timely manner under PCT Rule 17.1(a) has been acknowledged as evidenced by the attached PCT/IB/304.

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PCT/JP2004/005987

Australian Government

25.05.2004

Patent Office
Canberra

I, JULIE BILLINGSLEY, TEAM LEADER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003902208 for a patent by FUJISAWA PHARMACEUTICAL CO., LTD. as filed on 08 May 2003.

WITNESS my hand this
Twenty-ninth day of April 2004

J. Billingsley

JULIE BILLINGSLEY
TEAM LEADER EXAMINATION
SUPPORT AND SALES

Regulation 3.2

Fujisawa Pharmaceutical Co., Ltd.

A U S T R A L I A

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Inhibitor of Cox"

The invention is described in the following statement:

D E S C R I P T I O N

INHIBITOR OF COX

TECHNICAL FIELD

This invention relates to imidazole compounds and pharmaceutically acceptable salts thereof having pharmacological activity.

Moreover, this invention relates to medicament or pharmaceutical composition comprising the above mentioned imidazole compounds or pharmaceutically acceptable salts thereof as an active ingredient.

BACKGROUND ART

Some imidazole derivatives having anti-inflammatory and/or analgesic activities have been known, for example, WO 96/03388. However, all of example imidazole compounds disclosed in this document are substituted by sulfonyl groups. And the compounds disclosed in WO 96/03388 selectively inhibit cyclooxygenase-II (COX-II) over cyclooxygenase-I (COX-I). On the other hand, the imidazole compounds of this invention are not substituted by sulfonyl groups.

DISCLOSURE OF THE INVENTION

As a result of studies on the synthesis of imidazole compounds and their pharmaceutical activity, the inventors of this invention have found that the imidazole compounds of this invention have superior activity of inhibiting COX (especially, COX-I inhibiting activity). So, this invention relates to imidazole compounds, which have pharmaceutical activity such as COX inhibiting activity, to a medicament and a pharmaceutical composition containing the imidazole compounds.

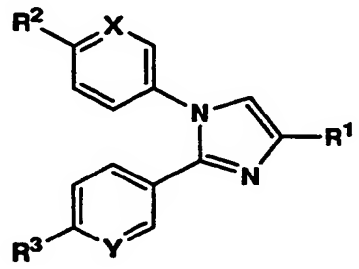
Accordingly, one object of this invention is to provide the imidazole compounds, which have a COX inhibiting activity.

Another object of this invention is to provide a method for treatment and/or prevention and the imidazole compounds for use

in the treatment and/or prevention of the disease associated with COX.

A further object of this invention is to provide a use of the imidazole compounds for manufacturing a medicament for treating or preventing the diseases and the analgesic agent comprising the imidazole compounds which is usable for treating and/or preventing pains.

The imidazole compounds of this invention can be represented by the following general formula (I):



(I)

wherein

R^1 is lower alkyl, halogen-substituted lower alkyl, hydroxy-substituted lower alkyl, cycloalkyl, carbamoyl, N-(lower alkyl)carbamoyl, N,N-di(lower alkyl)carbamoyl, formyl, lower alkanoyl, carboxy, (lower alkoxy)carbonyl, or cyano;

R^2 is halogen, cyano, hydroxy, lower alkoxy, aryl(lower alkyl)oxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is lower alkoxy, hydroxy, amino, (lower alkyl)amino, or di(lower alkyl)amino;

X and Y are each CH or N;

or pharmaceutically acceptable salts thereof.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

So, the "lower alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, or the like, and it is preferably C1-C4 alkyl, more preferably C1-C2 alkyl, most preferably methyl.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine atom and an iodine atom, and is preferably a fluorine atom or a chlorine atom, more preferably a chlorine atom.

The "halogen-substituted lower alkyl" means a monovalent group in which the above lower alkyl is subsutituted by 1 to 5 the above halogen atom(s), such as fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, trifluoromethyl, trichloromethyl, fluoroethyl, chloroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2,2,3,3,3-pentafluoroethyl, fluoropropyl, fluorobutyl, fluorohexyl, or the like, and it is preferably halogen-substituted C1-C4 alkyl, more preferably halogen-substituted C1-C2 alkyl, more preferably fluorine-substituted C1-C2, more preferably fluorine-substituted methyl, most preferably difluoromethyl or trifluoromethyl.

The "hydroxy-substituted lower alkyl" means a monovalent group in which the above lower alkyl is subsutituted by a OH group, such as hydroxymethyl, hydroxyethyl, hydroxypropyl, 1-hydroxyisopropyl, 2-hydroxyisopropyl, hydroxybutyl, hydroxyisobutyl, hydroxy-tert-butyl, hydroxyhexyl, or the like, and it is preferably hydroxy-substituted C1-C4 alkyl, more preferably hydroxy-substituted C1-C2 alkyl, most preferably hydroxymethyl.

The "cycloalkyl" means C3-C10 cycloalkyl group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, or the like, and it is preferably C3-C6 cycloalkyl, more preferably C3-C5 cycloalkyl, most preferably cyclopropyl.

The "N-(lower alkyl)carbamoyl" means a carbamoyl group

substituted by the above lower alkyl group on nitrogen atom, such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, tert-butylcarbamoyl, pentylcarbamoyl, hexylcarbamoyl, or the like, and it is preferably (C1-C4 alkyl)carbamoyl, more preferably (C1-C2 alkyl)carbamoyl.

The "N,N-di(lower alkyl)carbamoyl" means a carbamoyl group substituted by the same or different above lower alkyl groups on nitrogen atom, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl, dibutylcarbamoyl, diisobutylcarbamoyl, dipentylcarbamoyl, dihexylcarbamoyl, ethylmethylcarbamoyl, methylpropylcarbamoyl, butylmethylcarbamoyl, ethylpropylcarbamoyl, butylethylcarbamoyl, or the like, and it is preferably di(C1-C4 alkyl)carbamoyl, more preferably di(C1-C2 alkyl)carbamoyl.

The "lower alkanoyl" means carbonyl group which is substituted by the above lower alkyl groups, such as acetyl, propionyl, butyryl, pivaloyl, valeryl, isovaleryl, hexanoyl, or the like, and it is preferably C2-C5 alkanoyl, more preferably C2-C3 alkanoyl, most preferably acetyl.

The "lower alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, or the like, and it is preferably C1-C4 alkoxy, more preferably C1-C2 alkoxy, most preferably methoxy.

The "(lower alkoxy)carbonyl" means a $-CO_2-$(lower alkyl) group, such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, pentoxycarbonyl, hexoxycarbonyl, or the like, and it is preferably (C1-C4 alkoxy)carbonyl, more preferably (C1-C2 alkoxy)carbonyl.

The "aryl(lower alkyl)oxy," means the above mentioned lower alkoxy group which is substituted with aryl group, such as benzyloxy, nephtylmethyloxy, indenylmethyloxy, phenetyl, nephtylethyl, phenylpropyl, phenylbutyl, phenylhexyl, or the like, and it is preferably aryl(C1-C2 alkyl)oxy, more preferably arylmethoxy,

most preferably benzyloxy.

The "(lower alkyl)amino" means a amino group substituted by the above lower alkyl group, such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, tert-butylamino, pentylamino, hexylamino, or the like, and it is preferably (C1-C4 alkyl)amino, more preferably (C1-C2 alkyl)amino.

The "di(lower alkyl)amino" means a amino group substituted by the same or different above lower alkyl groups, such as dimethylamino, diethylamino, dipropylamino, diisopropylamino, dibutylamino, diisobutylamino, dipentylamino, dihexylamino, ethylmethylamino, methylpropylamino, butylmethylamino, ethylpropylamino, butylethylamino, or the like, and it is preferably di(C1-C4 alkyl)amino, more preferably di(C1-C2 alkyl)amino.

The combination of X and Y is X and Y are each CH, X is N and Y is CH, X is CH and Y is N, X and Y are each N, preferably X and Y are each CH, X is N and Y is CH, or X is CH and Y is N, and any of these three combination are preferable.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compounds of the formula (I) and its salts can be in a form of a solvate, which is included within the scope of the present invention. The solvate preferably include a hydrate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The imidazole compounds of this invention can be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional

non-toxic salts and include a metal salt such as an alkali metal salt (e.g., sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g., trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, etc.), an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like.

The imidazole compound (I) may preferably include wherein

R^1 is lower alkyl, halogen-substituted lower alkyl, cycloalkyl, N,N-di(lower alkyl)carbamoyl, lower alkanoyl, or cyano;

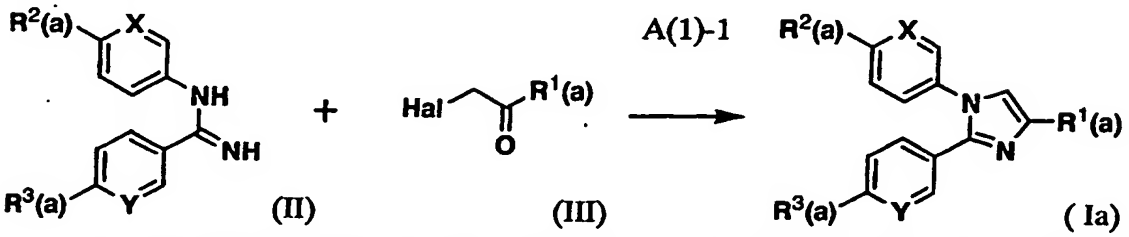
R^2 is halogen, cyano, hydroxy, or lower alkoxy;

R^3 is lower alkoxy;

X and Y are each CH, X is N and Y is CH, or X is CH and Y is N.

The compound of the formula (I) of the present invention can be prepared according to the following process.

Process A(1)



(II) (III) (Ia)

In the above formulae, X and Y represent the same meanings as defined above. R^1(a), R^2(a) and R^3(a) represent the group in the definition of R^1, R^2 and R^3, respectively, which do not influence this process. Concretely, R^1(a) represents lower alkyl, lower alkyl which is substituted with halogen, cycloalkyl, (lower alkoxy)carbonyl, or cyano; R^2(a) represents halogen, cyano, lower alkoxy, aryl(lower alkyl)oxy, or (lower alkoxy)carbonyl; R^3(a) represents is lower alkoxy. Hal represents halogen atom, especially, chlorine or bromine atom.

Process A(1) is the process for preparing the compound (Ia), which corresponds to compound (I) in which R^1 to R^3 are not reactive groups.

This process is carried out by reacting compound (II) and compound (III) in the presence of base to form imidazole ring.

Compound (II) may be purchased if it is commercial, or synthesized according to Processes B mentioned after or other general methods from commercial compounds. Compound (III) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because compound (III) as starting compound for synthesis of compound (Ia) have comparatively simple structure.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol, ethanol, 2-propanol; ethers such as diisopropyl ether, tatrahydrofuran, dioxane; and mixed solvent of these.

The base employable in this process for making basic condition

is not particularly limited so long as it accelerate this reaction and may include alkali metal hydrogencarbonates such as litium hydrogencarbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; alkali metal carbonates such as lithium carbonate, sodium carbonate and potassium carbonate; alkaline earth metal carbonates such as magnesium carbonate and calsium carbonate; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide, preferably alkali metal hydrogencarbonates, especially sodium hydrogencarbonate.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50 ℃ to 150℃, preferably from 60 ℃ to 100 ℃ or reflux condition.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 1day, preferably from 2hrs to 12hrs.

After the reaction, the reaction mixture is cooled to room temperature and evaporated in vacuo, then added water and extracted with organic solvent immiscible with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

According to the starting material, the heterocyclic ring is formed but not to form imidazole ring. In such case, the dehydration process is needed to form imidazole ring.

The dehydration process is carried out in the hot and acidic condition.

The solvent employable in this process is not particularly limited, but acid such as acetic acid, sulfuric acid or the like may be used as solvent.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50 ℃ to 200 ℃, preferably from 80 ℃ to 150 ℃.

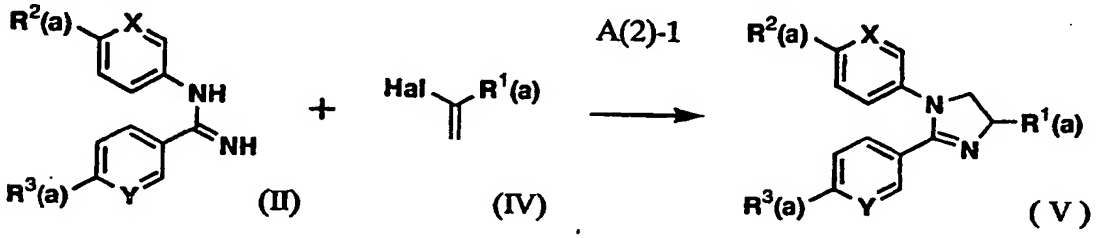
The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually

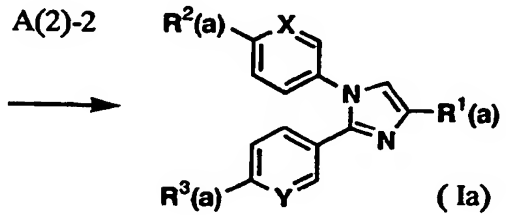
from 30min to 5hrs, preferably from 1hr to 3hrs.

After the reaction, the mixture is poured into basic water, and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

Compound (Ia) can also be synthesized according to the following process.

Process A(2)





In the above formulae, $R^1(a)$, $R^2(a)$, $R^3(a)$, X, Y and Hal represent the same meanings as defined above.

Process A(2) is the process for preparing the compound (Ia), which corresponds to compound (I) in which R^1 to R^3 are not reactive groups.

In this process, first, compound (II) is condensed to compound (IV) for synthesis of compound (V) (Process A(2)-1).

Process A(2)-1 is carried out under in the presence of Hunig's base (N,N-diisopropylethylamine).

Compound (IV) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because compound (IV) have comparatively simple structure.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diisopropyl ether, tatrahydrofuran, dioxane, preferably tetrahydrofuran.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50 ℃ to 200 ℃, preferably from 50 ℃ to 120 ℃ or reflux condition.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 2days, preferably 1hr to 5hrs or over night.

If the reaction does not proceed adequately, additional compound (IV) may be added.

After the reaction, the desired compound (Ia) is collected from the reaction mixture according to a conventional method. For example, after cooled to room temperature and evaporated in vacuo, the reaction mixture is poured into water and extracted with organic solvent immiscible with water such as ethyl acetate. The organic solvent is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo, and the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

Process A(2)-2 is the oxidation process to form imidazole ring in the presence of catalyst.

The oxidative catalyst employable in this process is not particularly limited so long as it can catalyze the reaction from 4,5-dihydro-imidazole derivative to imidazole derivative and may include manganese(IV) oxide (MnO_2).

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include amides such as N,N-dimethylformamide, dimethylacetamide, hexamethylphosphoric triamide; aromatic hydrocarbon such as benzene, toluene; or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50 ℃ to 200 ℃, preferably from 80 ℃ to 120 ℃ or reflux condition.

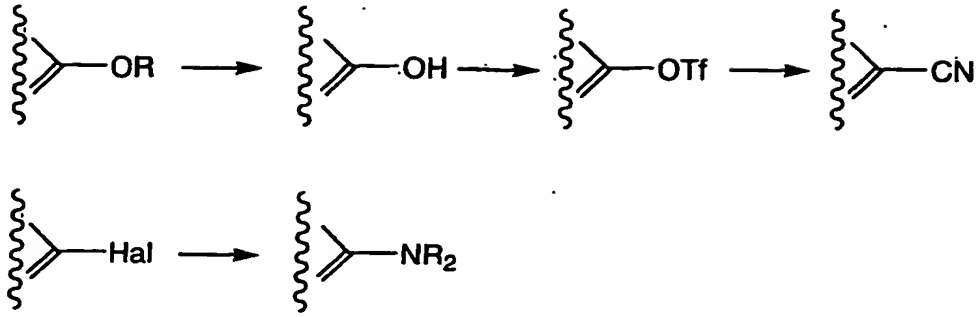
The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 24hrs, preferably 2hrs to 12hrs.

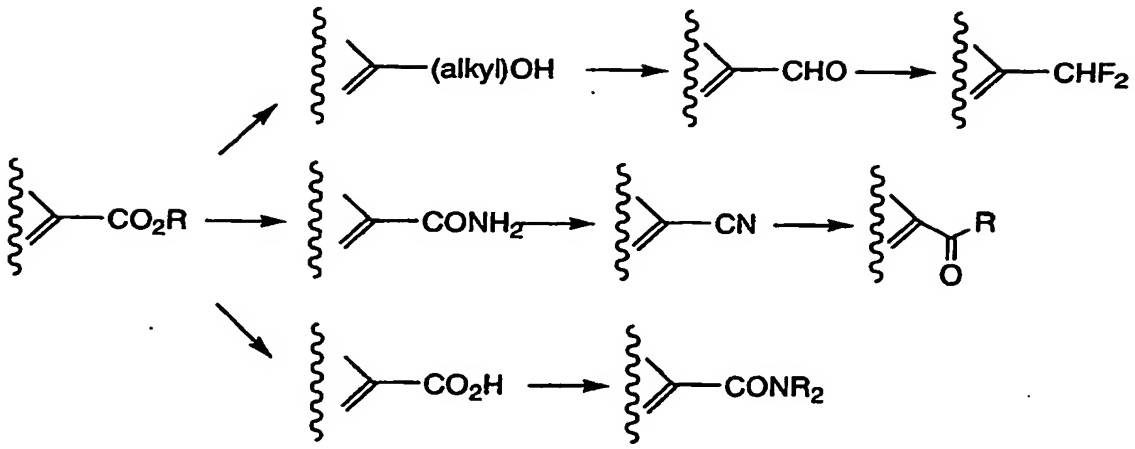
If the reaction does not proceed adequately, additional catalyst may be added.

After the reaction, the mixture is cooled to room temperature and filtered to remove catalyst. The organic fraction is concentrated in vacuo, or poured into basic water, and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is washed with water or the like, dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo. The desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc.

Compound (Ia) can be transformed into compound (I) by functional group trans formation, which is obvious to the person skilled in the organic chemistry. For example, such reactions are illustrated as following.

Process A(3)





In the above formulae, R represents H, lower alkyl or aryl(lower alkyl), which is not specified. Tf represents trifluoromethanesulfonyl as protective group.

4,5-Dihydoroimidazole compound (V) can be transformed into compound (IX) by the above mentioned functional group trans formation.

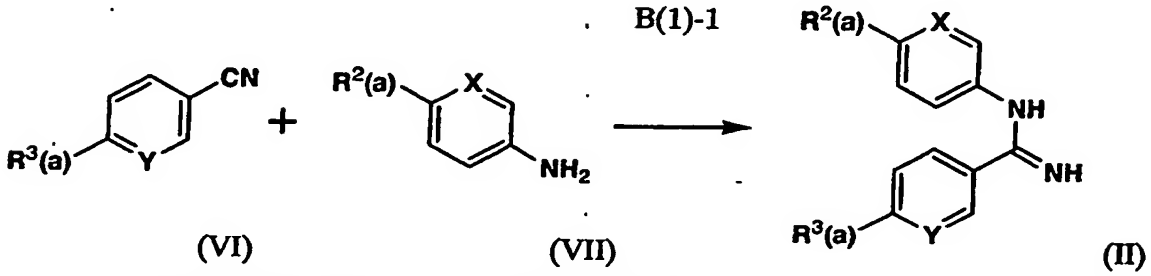
Process A(4)

(V) (IX)

Compound (IX) or pharmaceutically acceptable salts thereof also has an inhibiting activity against COX. So compound (IX) or salt thereof is also useful as medicament.

Compound (II) can be synthesized from compound (VI) and (VII) by following process other than purchase.

Process B(1)



(VI) (VII) (II)

In the above formulae, $R^2(a)$, $R^3(a)$, X and Y represent the same meanings as defined above.

Process B(1) is the process for preparing the compound (II), which is the starting material of Process A(1) and A(2).

Compound (VI) and (VII) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds, because the compounds as starting compound for synthesis of compound (II) have comparatively simple structure.

In this process, first, the solution of compound (VII) is added strong base.

The strong base employable in this process is not particularly limited and may include alkali metal hydrides such as lithium hydride, sodium hydride; alkali metal alkoxides such as lithium methoxide, sodium methoxide, sodium ethoxide, potassium t-butoxide; or the like.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diethyl ether, diisopropyl ether, tatrahydrofuran, dioxane; amides such as N,N-dimethylformamide, dimethylacetamide, hexamethylphosphoric triamide; sulfoxides such as dimethylsulfoxide; or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -10 ℃ to room temperature, preferably room temperature.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually

from 5min to 1hr, preferably from 10min to 40min.

Preferably, this process is carried out under inert gas such as nitrogen gas.

In this process, then the reaction mixture is added compound (VII).

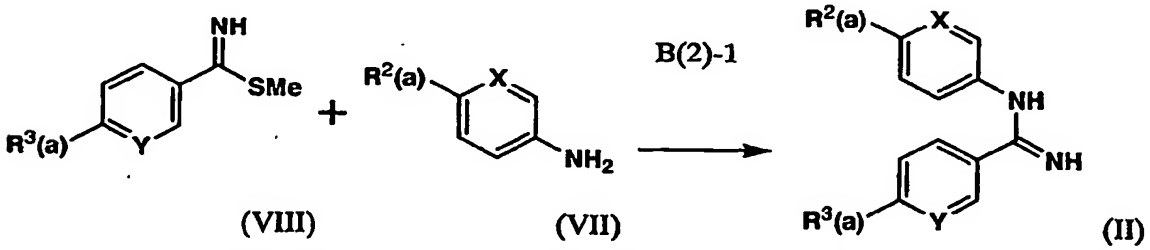
The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from -10 ℃ to room temperature, preferably room temperature.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 1hr to 24hrs, preferably from 2hrs to overnight.

After the reaction, the reaction mixture is poured into ice water to decompose the excess strong base. Then, the desired compound may be collected by filtration as precipitate. Where necessary, it may be washed by solvent such as diisopropyl ether. Further, the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc, however, it may be used in the next step without further purification.

Compound (II) can be also synthesized from compound (VII) and (VIII) by following process other than purchase.

Process B(2)



(VIII) (VII) (II)

In the above formulae, $R^2(a)$, $R^3(a)$, X and Y represent the same meanings as defined above.

Process B(2) is the another process for preparing the compound (II), in the case that $R^3(a)$ is the group such as alkoxy carbonyl or the like, which tends to be nucleophilically attacked more easily than cyano group.

In this process, compound (VII) and (VIII) are condensated

in the acidic condition.

Compound (VII) may be purchased if it is commercial, or synthesized according to general methods from commercial compounds.

Compound (VIII) may be synthesized by conventional method, that is, first the nitrile compound is led to tioamide compound by thioacetamide, and then methylated.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as alcohols such as methanol, ethanol, 2-propanol; ethers such as diisopropyl ether, tatrahydrofuran, dioxane; and mixed solvent of these; or the like.

The acid for making acidic condition in this process is not particularly limited so long as it is used in a usual reaction as an acid catalyst and may include inorganic acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, or the like.

The reaction temperature varies depending on the starting material, the solvent, etc., but it is usually from 50℃ to 150℃, preferably reflux condition.

The reaction time varies depending on the starting material, the solvent, the reaction temperature, etc., but it is usually from 30min to 5hrs, preferably from 2hrs to 4hrs.

After the reaction, the reaction mixture is poured into basic water and extracted with organic solvent insoluble with water such as ethyl acetate. The organic layer is dried over anhydrous magnesium sulfate or sodium sulfate, evaporated in vacuo. Where necessary, it may be washed by solvent such as diisopropyo ether. Further, the desired compound is purified by the conventional method such as silica gel column chromatography, recrystallization, etc, however, it may be used in the next step without further purification.

Above processes (Process A and B), all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional

method.

For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

THE BEST MODE FOR CARRYING OUT THE INVENTION

The patents, patent applications and publications cited herein are incorporated by reference.

The following Examples and Preparations are given only for the purpose of illustrating the present invention in more detail.

Example 1-1

N^1-(4-Bromophenyl)-4-methoxybenzamidine

Under Nitrogen gas, to a solution of 4-bromoaniline (3.88g, 22.5mmol) in dimethylsulfoxide (30ml) was added NaH (568mg, 23.7mmol) at room temperature. After the mixture was stirred for 30min, 4-methoxybenzonitrile (3.0g, 22.5mmol) was added. The reaction mixture was stirred overnight then poured into 300ml of ice-water. The precipitate was collected by filtration and washed with isopropyl ether to give 5.53g of desired compound as a white solid (80.4%).

IR (KBr, cm^{-1}) : 3473, 3357, 2958, 1612, 1249, 1174, 1103, 1074, 1030, 837.

NMR (DMSO-d_6, δ) : 3.80(3H, s), 6.32(2H, brs), 6.78(2H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.42(1H, d, J=8Hz), 7.92(2H, d, J=8Hz).

MS : 305 $(M+H)^+$ (^{79}Br), 307 $(M+H)^+$ (^{81}Br).

Example 1-2

1-(4-Bromophenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

To a mixture of N^1-(4-Bromophenyl)-4-methoxybenzamidine obtained by Example 1-1 (2.0g, 6.55mmol) and sodium bicarbonate (826mg, 9.83mmol) in 2-propanol (20ml) was added 3-bromo-1,1,1-trifluoro-2-propanone (2.0g, 10.5mmol). The reaction mixture was heated at 80℃ for 2hrs. The reaction mixture was cooled to room temperature and filtered. The organic layer

was evaporated in vacuo. The residue in acetic acid (20ml) was heated at 110℃ for 2.5hrs. The reaction mixture was poured into ice-water (100ml) and neutralized with sodium hydroxide aq. and extracted with ethyl acetate (50ml). The organic layer was washed with brine, dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (20g) eluting with n-hexane/ethyl acetate (10/1) and washed with diisopropyl ether to give 660mg of desired compound (25.4%).

MP : 140-141℃.

IR (KBr, cm^{-1}) : 3140, 2970, 1487, 1294, 1252, 1149, 1122, 1026, 833.

NMR (DMSO-d_6, δ) : 3.75(3H, s), 6.92(2H, d, J=9Hz), 7.27(2H, d, J=9Hz), 7.36(2H, d, J=9Hz), 7.71(2H, d, J=2Hz), 8.18(1H, s).

MS : 397 $(M+H)^+$ (^{79}Br), 399 $(M+H)^+$ (^{81}Br).

Example 2-1

4-Methoxy-N^1-(2-Methoxy-5-pyridyl)benzamidine

Reaction was carried out in a manner similar to Example 1-1 using 4-methoxybenzonitrile and 5-amino-2-methoxypyridine to give 4.57g of desired compound (78.8%).

IR (KBr, cm^{-1}) : 3452, 3334, 3205, 2946, 1606, 1483, 1273, 1246, 1176, 1028, 841.

NMR (DMSO-d_6, δ) : 3.80(3H, s), 3.82(3H, s), 6.36(2H, brs), 6.76(1H, d, J=9Hz), 6.96(2H, d, J=9Hz), 7.20(1H, dd, J=9Hz and 3Hz), 7.67(1H, d, J=3Hz), 7.94(2H, d, J=9Hz).

MS : 258 $(M+H)^+$.

Example 2-2

2-(4-Methoxyphenyl)-1-(2-methoxy-5-pyridyl)-4-trifluoromethy 1-1H-imidazole hydrochloride

Reaction was carried out in a manner similar to Example 1-2

using 4-Methoxy-N^1-(2-Methoxy-5-pyridyl)benzamidine obtained by Example 2-1 to give 2-(4-Methoxyphenyl)-1-(2-methoxy-5-pyridyl)-4-trifluoromethy l-1H-imidazole. And then the product obtained was dissolved in ethyl acetate and treated with 4N hydrogen chloride in ethyl acetate to give 399mg of desired compound as a white amorphous solid (14.7%).

NMR (DMSO-d_6, δ) : 3.75(3H, s), 3.89(3H, s), 6.80-7.05(3H, m), 7.31(2H, d, J=9Hz), 7.43(1H, d, J=9Hz), 7.74(1H, dd, J=9Hz and 2Hz), 8.17(1H, s), 8.27(1H, s).
MS : 350 $(M+H)^+$ (free).

Example 3-1
N^1-(4-Methoxyphenyl)-2-methoxy-5-amidinopyridine

Under Nitrogen gas, to a solution of p-anisidine (2.75g, 22.4mmol) in tetrahydrofuran (15ml) was added dropwise 1.0M sodium bis(trimethylsilyl)amide in tetrahydrofuran (23.5ml, 23.5mmol) at room temperature. After the mixture was stirred for 20min, 6-methoxynicotinonitrile (3.0g, 22.4mmol) was added. The reaction mixture was stirred for 4hrs, then poured into 300ml of ice-water. The precipitate was collected by filtration, washed with diisopropyl ether to give 3.36g of desired compound (58.4%) (mixture).

This material was used without further purification.

NMR (DMSO-d_6, δ) : 3.73(3H, s), 3.90(3H, s), 6.27(2H, brs), 6.70-7.00(5H, m), 8.24(1H, dd, J=9Hz and 2Hz), 8.72(1H, d, J=2 Hz).
MS : 258 $(M+H)^+$.

Example 3-2
1-(4-Methoxyphenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromethy l-1H-imidazole

Reaction was carried out in a manner similar to Example 1-2 using N^1-4-Methoxy-2-methoxy-5-amidinopyridine obtained by Example 3-1 to give 526.6mg of desired compound as a colorless crystal (21.5%).

MP : 90-92℃.

IR (KBr, cm^{-1}) : 3141, 3107, 1604, 1518, 1294, 1248, 1159, 1118, 835.

NMR (DMSO-d_6, δ) : 3.81(3H, s), 3.83(3H, s), 6.81(1H, d, J=9Hz), 7.05(2H, d, J=9Hz), 7.38(2H, d, J=9Hz), 7.65(1H, dd, J=9Hz and 2Hz), 8.08(1H, d, J=2Hz), 8.17(1H, s).

MS : 350 $(M+H)^+$.

Example 4-1

4-Cyano-4,5-dihydro-1-(4-Methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole

To a suspension of N^1-4-Methoxy-2-methoxy-5- amidinopyridine obtained by Example 3-1 in tetrahydrofuran (20ml) were added 2-chloroacrylonitrile and diisopropylethylamine successively. The reaction mixture was heated at 70℃. After 5hrs, an additional 1.07ml of 2-chloroacrylonitrile was added and refluxed overnight. The reaction mixture was cooled to room temperature, filtered and the solvent was removed in vacuo. The crude mixture was purified by silica gel column chromatography (24g) eluting with ethyl acetate to give 460mg of desired compound (54.9%).

This material was used in Example 4-2 without further purification.

Example 4-2

4-Cyano-1-(4-Methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole

A suspension of the residue and manganese(IV) oxide (MnO_2) (1.3g, 10eq) in toluene (10ml) was heated at 85℃ for 5.5hrs. To

the reaction mixture was added manganese(IV) oxide (0.65g, 5eq) and heated at 110℃ for 3hrs. After cooling, the mixture was filtered through a Celite. The organic fraction was concentrated (396mg). The crude mixture was purified by silica gel column chromatography (12g) eluting with chloroform/methanol (50/1→15/1) and washed with diisopropyl ether to give 200.8mg of desired compound as a colorless solid (24.1%, through Example 4-1 and 4-2).

MP : 130-132℃.

IR (KBr, cm^{-1}) : 3132, 2949, 2233, 1604, 1516, 1466, 1292, 1254, 1024, 835.

NMR (DMSO-d_6, δ) : 3.81(3H, s), 3.84(3H, s), 6.81(1H, d, J=9Hz), 7.06(2H, d, J=9Hz), 7.37(2H, d, J=9Hz), 7.62(1H, dd, J=9Hz and 2Hz), 8.10(1H, d, J=2Hz), 8.47(1H, s).

MS : 307 $(M+H)^+$.

Example 5-1

N^1-(4-Benzyloxyphenyl)-2-methoxy-5-amidinopyridine

Reaction was carried out in a manner similar to Example 3-1 using 4-benzyloxyaniline hydrochloride to give 8.7g of desired compound (71.7%).

IR (KBr, cm^{-1}) : 3488, 3396, 3031, 2958, 1635, 1502, 1373, 1236, 1103, 1020, 840.

NMR (DMSO-d_6, δ) : 3.90(3H, s), 5.06(2H, s), 6.28(2H, brs), 6.70-7.05(5H, m), 7.25-7.60(5H, m), 8.24(1H, dd, J=9Hz and 2Hz), 8.72(1H, d, J=2Hz).

MS : 334 $(M+H)^+$.

Example 5-2

1-(4-Benzyloxyphenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromethyl-1H-imidazole

Reaction was carried out in a manner similar to Example 1-2 using N^1-(4-Benzyloxyphenyl)-2-methoxy-5-amidinopyridine obtained by Example 5-1 to give 2.27g of desired compound (44.5%).

IR (KBr, cm^{-1}) : 3064, 2950, 1290, 1244, 1157, 1122, 1022, 835.
NMR (DMSO-d_6, δ) : 3.84(3H, s), 5.16(2H, s), 6.81(1H, d, J=9Hz), 7.05-7.58(9H, m), 7.65(1H, dd, J=9Hz and 2Hz), 8.08(1H, d, J=2Hz), 8.17(1H, s).
MS : 426 $(M+H)^+$.

Example 6-1
1-(4-Hydroxyphenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromethy 1-1H-imidazole

To a solution of 1-(4-benzyloxyphenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromet hyl-1H-imidazole obtained by Example 5-2 (2.25g, 5.29mmol) in cyclohexene (22ml) and ethanol (45ml) was added 20% palladium hydroxide on carbon (550mg). The resulting mixture was stirred at reflux for 2hrs. After cooling to room temperature, the mixture was filtered through Celite and washed with ethanol. The filtrate was concentrated in vacuo, and then the residue was washed with diisopropyl ether to give 1.31g of desired compound as a white solid (73.9%).

MP : 198-200℃.
IR (KBr, cm^{-1}) : 3600-2600, 1469, 1292, 1247, 1159, 1126, 833.
NMR ($CDCl_3$, δ) : 3.91(3H, s), 6.67(1H, brs), 6.73(1H, d, J=9Hz), 6.87(2H, d, J=9Hz), 7.11(2H, d, J=9Hz), 7.43(1H, s), 7.86(1H, dd, J=9Hz and 2Hz), 8.03(1H, d, J=2Hz).
MS : 336 $(M+H)^+$.

Example 7-1
2-(2-Methoxy-5-pyridyl)-1-(4-trifluoromethanesulfonyloxyphen yl)-4-trifluoromethyl-1H-imidazole

To the mixture of 1-(4-hydroxyphenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromethy 1-1H-imidazole obtained by Example 6-1 (600mg, 1.79mmol) and triethylamine (190mg, 1.88mmol) in chloroform (12ml) was added trifluoromethanesulfonic anhydride dropwise at an ice bath temperature and stirred for 4.5hrs. Sodium hydrogencarbonate aq. (10ml) was added to quench the reaction. The reaction mixture was partitioned between chloroform and water. The organic layer was washed with water and then brine, dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (10g) eluting with n-hexane/ethyl acetate (10/1) to give 593mg of desired compound (70.9%).

IR (KBr, cm^{-1}) : 3118, 3062, 1421, 1255, 1219, 1136, 891.
NMR ($CDCl_3$, δ) : 3.92(3H, s), 6.71(1H, d, J=9Hz), 7.30-7.48(4H, m), 7.50(1H, s), 7.66(1H, dd, J=9Hz and 2Hz), 8.08(1H, d, J=2Hz).
MS : 467 $(M+H)^+$.

Example 7-2
1-(4-Cyanophenyl)-2-(2-methoxy-5-pyridyl)-4-trifluoromethyl-1H-imidazole

To a solution of 2-(2-methoxy-5-pyridyl)-1-(4-trifluoromethanesulfonyloxyphen yl)-4-trifluoromethyl-1H-imidazole obtained by Example 7-1 (150mg, 0.321mmol) in N,N-dimethylformamide (7.5ml) were added zinc cyanide ($Zn(CN)_2$) (38mg, 0.321mmol) and tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) (185mg, 0.16mmol) at ambient temperature under nitrogen gas. The mixture was stirred at 85℃ for 2days. The mixture was cooled to room temperature and partitioned between ethyl acetate (50ml) and water (50ml). The organic layer was washed with water and brine, then dried by magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography (20g) eluting

with toluene/ethyl acetate (10:1) and washed with diisopropyl ether to give 57.2mg of desired compound as a white solid (51.8%).

MP : 155-158℃.

IR (KBr, cm^{-1}) : 3120, 2250, 1606, 1250, 1122, 822.

NMR (DMSO-d_6, δ) : 3.85(3H, s), 6.82(1H, d, J=9Hz), 7.61(1H, dd, J=9Hz and 2Hz), 7.65(2H, d, J=9Hz), 8.03(2H, d, J=9Hz), 8.12(1H, d, J=2Hz), 8.36(1H, s).

MS : 345 $(M+H)^+$.

Example 8-1

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of N^1-(4-methoxyphenyl)-4-methoxybenzamidine (0.65 g), ethyl bromopyruvate (0.64 ml) and sodium hydrogencarbonate (0.85 g) in ethanol (7 ml) was stirred at reflux condition for overnight. After cooling to room temperature, the reaction mixture was filtrated and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5/1→2/1) to give 244mg of desired compound as an oil (27.3%).

IR (Neat, cm^{-1}) : 3437, 3392, 3367, 3217, 3140, 3072, 2966, 2843, 1803, 1699, 1651, 1614.

NMR (DMSO-d_6, δ) : 1.29(3H,t, J=7.1Hz), 3.74(3H, s), 3.80(3H, s), 4.27(2H, q, J=7.1Hz), 6.88(2H, dd, J=6.8Hz and 2.1Hz), 7.02(2H, dd, J=6.7Hz and 2.1Hz), 7.26 (2H, dd, J=5.0Hz and 2.1Hz), 7.28 (2H, dd, J=6.7Hz and 2.1Hz), 8.02 (1H, s).

MS : 353 $(M+H)^+$.

Example 9-1

4-Carbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imida

zole

A mixture of 4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 8-1 (244mg) and sodium methoxide (112mg) in formamide (2ml) was stirred at 100℃ for 2hrs. After cooling to room temperature, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1→0/1) to give 73mg of desired compound (32.6%).

MP : 167-169℃.
IR (KBr, cm^{-1}): 3427, 3342, 3276, 3155, 2964, 2841, 1672, 1610.
NMR (DMSO-d_6, δ) : 3.74(3H, s), 3.80(3H, s), 6.87-6.89(2H, m), 7.00-7.03(2H, m), 7.20(1H, s), 7.26-7.29(4H, m), 7.43(1H, s), 7.77(1H, s).
MS : 324 $(M+H)^+$.

Example 10-1
4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

A mixture of 4-carbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 9-1 (73mg) and phosphorus oxychloride (63μl) in N,N-dimethylformamide (1ml) was stirred at room temperature for 1hr. The reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (2/1).

After correcting the fraction, the solvent was removed by evaporation and the residue was dissolved in ethyl acetate (1ml). 4N Hydrochloride/ethyl acetate (56ml) was added to the above

solution. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 38mg of desired compound (49.2%).

MP : 142-143℃.

IR (KBr, cm^{-1}): 3425, 3407, 3132, 3076, 3043, 3026, 2962, 2929, 2835, 2231, 1608.

NMR (DMSO-d_6, δ) : 3.74(3H, s), 3.80(3H, s), 6.55(1H, s), 6.88-6.91(2H, m), 7.03-7.05(2H, m), 7.25-7.32(4H, m), 8.39(1H, s).

MS : 306 (free) $(M+H)^+$.

Example 11-1

4-Cyano-4,5-dihydro-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of N^1-(4-methoxyphenyl)-4-methoxybenzamidine (5g), 2-chlorocyanoethylene (2.01ml) and N,N-diisopropylethylamine (4.38 ml) in tetrahydrofuran (100ml) was stirred at reflux condition for 6hrs. Additional 2-chlorocyanoethylene (2.01ml) was added, the mixture was refluxed for overnight. After cooling to room temperature, the reaction mixture was evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 3.28 g of desired compound as an oil (63.7%).

IR (Neat, cm^{-1}) : 3283, 3217, 3114, 3055, 3003, 2958, 2839, 2243, 2048, 1896, 1732, 1606.

NMR (DMSO-d_6, δ) : 3.70(3H, s), 3.74(3H, s), 4.11-4.19(2H, m), 5.20(1H, dd, J=10.5Hz and 8.2Hz), 6.81-6.97(6H, m), 7.32-7.37(2H, m).

MS : 308 $(M+H)^+$.

Example 11-2

4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A suspension of 4-cyano-4,5-dihydro-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 11-1 (2.7g) and manganese(IV) oxide (MnO_2) (3.82 g) in N,N-dimethylformamide (30ml) was stirred at 100℃ for 4hrs. After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. To the solution of the residue in N,N-dimethylformamide (30ml), phosphorus oxychloride (2.46ml) was added under stirring at 0℃. After stirring at room temperature for 1hr, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo to give 2.11g of desired compound (78.7%).

MP : 132-134℃.

NMR (DMSO-d_6, δ) : 3.74(3H, s), 3.80(3H, s), 6.87-6.93(2H, m), 7.02-7.08(2H, m), 7.23-7.34(4H, m), 8.39(1H, s).

MS : 306 $(M+H)^+$.

Example 12-1

4-Cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

4N Hydrochloride/ethyl acetate (254μl) was added to a solution of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 11-2 (300mg) in ethyl acetate (1ml). Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 300mg of desired compound (86.4%).

MP : 142-143℃.

IR (KBr, cm^{-1}) : 3425, 3407, 3132, 3076, 3043, 3026, 2962, 2929, 2835, 2231, 1608.

NMR (DMSO-d_6, δ) : 3.74(3H, s), 3.80(3H, s), 6.55(1H, s), 6.88-6.91(2H, m), 7.03-7.05(2H, m), 7.25-7.32(4H, m), 8.39(1H, s).

MS : 306 (free) $(M+H)^+$.

Example 13-1

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (315mg) and 4N hydrochloride/ethanol (6.2ml) was stirred at reflux condition for 1hr. After cooling to room temperature, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.26g of desired compound (71.5%).

MP : 142-143℃.

IR (Neat, cm^{-1}) : 3437, 3392, 3367, 3217, 3140, 3072, 2966, 2843, 1803, 1699, 1651, 1614.

NMR (DMSO-d_6, δ) : 1.29(3H,t, J=7.1Hz), 3.74(3H, s), 3.80(3H, s), 4.27(2H, q, J=7.1Hz), 6.88(2H, dd, J=6.8Hz and 2.1Hz), 7.02(2H, dd, J=6.7Hz and 2.1Hz), 7.26(2H, dd, J=5.0Hz and 2.1Hz), 7.28(2H, dd, J=6.7Hz and 2.1Hz), 8.02(1H, s).

MS : 353 $(M+H)^+$.

Example 13-2

4-Hydroxymethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

1N Diisopropylalminiumhydride in toluene (3.76ml) was added dropwise to a solution of

4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 13-1 (5ml) under stirring at -78℃, and stirred at -78℃ for 2hrs. The reaction mixture was quenched by sat. ammonium chloride aq., then 1N hydrochloric acid was added and extracted with water. The combined aqueous layer was neutralized with sat. sodium hydrogencarbonate aq., and extracted with ethyl acetate, dried over magnesium sulfate. After evaporation of the solution, the residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.14g of desired compound (30%).

IR (Neat, cm^{-1}) : 3369, 3307, 3224, 3076, 3006, 2939, 2837, 1676, 1608.

NMR (DMSO-d_6, δ) : 3.73(3H, s), 3.79(3H, s), 4.42(2H, d, J=5.6Hz), 4.96(1H, t, J=5.6Hz), 6.85(2H, d, J=8.8Hz), 7.00(2H, d, J=8.9Hz), 7.15-7.25(5H, m).

MS : 311 $(M+H)^+$.

Example 14-1

4-Formyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

Dimethylsulfoxide (125μl) was added to a solution of oxalylchloride (118μl) in dichloromethane (2ml) under stirring at -78℃. After stirred at -78℃ for 10min, a solution of 4-hydroxymethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 13-2 (0.21g) in dichloromethane (2ml) was added and stirred at -78℃ for 1hr. Triethylamine (0.66ml) was added to the reaction mixture, and stirred at 0℃ for 20min. The mixture was quenched by sat. ammonium chloride aq., and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo to give 120mg of desired compound as an oil (57.5%).

IR (Neat, cm^{-1}) : 3126, 3057, 3005, 2960, 2837, 2760, 2551, 2048, 1685, 1610.

NMR ($CDCl_3$, δ) : 3.83(3H, s), 3.86(3H, s), 6.81(2H, dd, J=6.9Hz and 2.0Hz), 6.94(2H, dd, J=6.8Hz and 2.1Hz), 7.16(2H, dd, J=6.7Hz and 2.2Hz), 7.36(2H, dd, J=6.7Hz and 2.1Hz), 7.16(1H, s), 9.98(1H, s).

MS : 309 $(M+H)^+$.

Example 15-1

4-Difluoromethyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

Diethylaminosulfur trifluoride (154μl) was added to a solution of 4-formyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 14-1 (120mg) in dicloromethane (2ml) under stirring at 0℃. After stirring at room temperature for overnight, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1). After correcting the fraction, the solvent was removed by evaporation and the residue was dissolved in ethyl acetate (1ml). 4N hydrochloride/ethyl acetate (97μl) was added. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 24mg of desired compound (16.8%).

MP : 150-153℃.

IR (KBr, cm^{-1}) : 3454, 3433, 3265, 3101, 3060, 2958, 2837, 2735, 2659, 2563, 1606.

NMR (DMSO-d_6, δ) : 3.76(3H, s), 3.80(3H, s), 6.84(1H, t, J=56.2Hz), 6.91-6.97(2H, s), 7.02-7.08(2H, m), 7.28-7.38(4H, m), 7.93 (1H, t, J=2.2Hz).

MS : 331 (free) $(M+H)^+$.

Example 16-1

4-Carboxy-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (1.5g) in 50% sulfuric acid (16ml) was stirred at reflux condition for 1hr. After cooling to room temperature, the reaction mixture was poured into 6% sodium hydroxide aq. (100ml), and washed with ethyl acetate. The aqueous layer was acidified by conc. hydrochloric acid and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The resulting precipitates were corrected by filtration and washed with isopropyl ether to give 1.18g of desired compound (74.1%).

MP : 102-105℃.

IR (KBr, cm^{-1}) : 3427, 3269, 3174, 3141, 3086, 3005, 2965, 2910, 2839, 1678, 1610.

NMR (DMSO-d_6, δ) : 3.76(3H, s), 3.813(3H, s), 6.89(2H, dt, J=7.0Hz and 2.0Hz), 7.03(2H, dt, J=7.2Hz and 2.0Hz), 7.26-7.32(4H, m), 7.97(1H, s).

MS : 325 $(M+H)^+$.

Example 17-1

4-Ethylmethycarbamoyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of 4-carboxy-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 16-1 (170mg), N-ethylmethylamine (45μl), 1-hydroxybenzotriazole (71mg) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (100mg) in N,N-dimethylformamide (5ml) was stirred at room

temperature for overnight. The reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1). The resulting precipitates were corrected by filtration and washed with isopropyl ether to give 72mg of desired compound (37.6%).

MP : 138-139 ℃.

IR (KBr, cm^{-1}) : 3124, 3068, 3006, 2966, 2929, 2841, 1603.

NMR (DMSO-d_6, δ) : 1.05-1.29(3H, m), 2.91-3.03(2H, m), 3.33-3.56(2H, m), 3.74(3H, s), 3.80(3H, s), 3.91-4.06(1H, m), 6.88(2H, dt, J=8.8Hz and 1.8Hz), 7.02(2H, dt, J=8.8Hz and 2.0Hz), 7.23-7.30(4H, m), 7.72(1H, s).

MS : 366 $(M+H)^+$.

Example 18-1

4-Cyclopropyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole hydrochloride

A mixture of N^1-(4-methoxyphenyl)-4-methoxybenzamidine (1g), 2-bromo-1-cyclopropylethanone (1.27g) and sodium hydrogencarbonate (656mg) in 2-propanol (10ml) was stirred at reflux condition for overnight. After cooling to room temperature, the reaction mixture was filtered off and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in acetic acid (10ml), and refluxed for 1hr. After cooling to room temperature, the mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hxane/ethyl acetate (3/1). After correcting the fraction, the solvent was removed by evaporation and the residue was dissolved in ethyl acetate (5ml). 4N

hydrochloride/ethyl acetate (175μl) was added. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 200mg of desired compound (14.4%).

MP : 180-181℃.

IR (KBr, cm^{-1}) : 3273, 3051, 2966, 2935, 2906, 2835, 2740, 2640, 2592, 1610.

NMR (DMSO-d_6, δ) : 0.88-0.96(2H, m), 1.00-1.07(2H, m), 2.02-2.11(2H, m), 3.79(3H, s), 3.80(3H, s), 7.00-7.11(4H, m), 7.35-7.41(4H, m), 7.67(1H, s).

MS : 321 (free) $(M+H)^+$.

Example 19-1

1-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-4-methyl-1H-imidazole hydrochloride

85mg of desired compound was obtained from N^1-(4-methoxyphenyl)-4-methoxybenzamidine (200mg) and 1-bromoacetone (204μl) in the similar manner that of Example 18-1.

MP : 203-205℃.

IR (KBr, cm^{-1}) : 3400, 3114, 3055, 2966, 2929, 2833, 2804, 2711, 2650, 2578, 2426, 1612.

NMR (DMSO-d_6, δ) : 2.39(3H, s), 3.79(3H, s), 3.81(3H, s), 7.02-7.12(4H, m), 7.36-7.66(4H, m), 7.66(1H, s), 14.6-15.5(1H, br).

MS : 295 (free) $(M+H)^+$.

Example 20-1

N^1-(4-Ethoxycarbonylphenyl)-4-methoxybenzamidine

A mixture of methyl 4-methoxybenzenecarbimidothioate hydroiodide (3.9g), ethyl 4-aminobenzoate (2.08g) and acetic acid

(2ml) in 2-propanol (40ml) was stirred at reflux condition for 2hrs. After cooling to room temperature, the reaction mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. Resulting precipitates were corrected by filtration and washed with isopropyl ether to give 2.35g of desired compound (62.4%).

MP : 128-132℃.

IR (KBr, cm^{-1}) : 3456, 3305, 3251, 3178, 2976, 2933, 2850, 1711, 1626.

NMR (DMSO-d_6, δ) : 1.31(3H, t, J=7.1Hz), 3.81(3H, s), 4.28(2H, q, J=7.1Hz), 6.46(2H, s), 6.90-7.01(4H, m), 7.86-7.91(4H, m).

MS : 299 $(M+H)^+$.

Example 20-2

1-(4-Ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

A mixture of N^1-(4-Ethoxycarbonylphenyl)-4-methoxybenzamidine obtained by Example 20-1 (0.5g), 3-bromo-1,1,1-trifluoro-2-propanone (0.35ml) and sodium hydrogencarbonate (563mg) in 2-propanol (5ml) was stirred at reflux condition for 4hrs. After cooling to room temperature, the reaction mixture was filtered off and evaporated in vacuo. Then the residue was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in acetic acid (10ml), and refluxed for 1hr. After cooling to room temperature, the mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (3/1) to give 0.53g of desired compound as an oil (81%).

IR (Neat, cm^{-1}) : 3745, 3610, 3435, 3396, 3365, 3298, 3280, 3236, 3130, 2962, 2927, 2856, 1693, 1649.

NMR (DMSO-d_6, δ) : 1.33(3H, t, J=7.1Hz), 3.75(3H, s), 4.34(2H, q, J=7.1Hz), 6.91(2H, dd, J=6.9Hz and 1.9Hz), 7.26(2H, dd, J=6.8Hz and 2.0Hz), 7.53 (2H, dd, J=6.8Hz and 1.7Hz), 8.04 (2H, dd, J=6.7Hz and 1.8Hz), 8.25 (1H, d, J=1.2Hz).

MS : 391 $(M+H)^+$.

Example 21-1

1-(4-Carbamoylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

255mg of desired compound was obtained from 1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Example 20-2 (710mg) in the similar manner that of Example 9-1.

IR (KBr, cm^{-1}) : 3410, 3303, 3190, 3122, 2960, 2841, 1655, 1614.

NMR (DMSO-d_6, δ) : 3.77(3H, s), 6.90(2H, dt, J=8.8Hz and 2.0Hz), 7.26(2H, dt, J=8.8Hz and 2.1Hz), 7.46(2H, d, J=8.5Hz), 7.52(1H, s), 7.96(2H, d, J=8.5Hz), 8.10(1H, s), 8.21(1H, d, J=1.2Hz).

MS : 362 $(M+H)^+$.

Example 22-1

1-(4-Cyanophenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole

A mixture of 1-(4-carbamoylphenyl)-2-(4-methoxyphenyl)-4-trifluoromethyl-1H-imidazole obtained by Example 21-1 (200mg) and phosphorus oxychloride (0.16ml) in N,N-dimethylformamide (2ml) was stirred at room temperature for 1hr. The reaction mixture was poured into saturated sodium hydrogencarbonate aq. and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. Resulting precipitates were corrected by filtration and

washed with isopropyl ether to give 171mg of desired compound (90%).

MP : 146-148℃.

IR (KBr, cm^{-1}) : 3415, 3163, 3118, 3064, 3012, 2968, 2906, 2839, 2229, 1608.

NMR (DMSO-d_6, δ) : 3.76(3H, s), 6.92(2H, dt, J=8.9Hz and 1.9Hz), 7.25(2H, dt, J=8.7Hz and 2.0Hz), 7.60(2H, dt, J=8.5Hz and 1.8Hz), 8.00(2H, dt, J=8.6Hz and 1.7Hz), 8.27(1H, d, J=1.1Hz).

MS : 344 $(M+H)^+$.

Example 23-1

4-Cyano-4,5-dihydro-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole

265mg of desired compound was obtained from N^1-(4-ethoxycarbonylphenyl)-4-methoxybenzamidine (500 mg) in the similar manner that of Example 11-1.

IR (Neat, cm^{-1}) : 3417, 3253, 3217, 3068, 2974, 2902, 2841, 1711, 1603.

NMR (DMSO-d_6, δ) : 1.28(3H, t, J=7.1Hz), 3.78(3H, s), 4.26(2H, q, J=7.1Hz), 4.31-4.46(2H, m), 5.27(1H, t, J=9.9Hz), 6.88-6.97(4H, m), 7.37(2H, dt, J=8.8Hz and 1.9Hz), 7.79 (2H, dt, J=8.7Hz and 1.9Hz).

MS : 350 $(M+H)^+$.

Example 23-2

4-Cyano-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A suspension of 4-cyano-4,5-dihydro-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 23-1 (0.26g) and manganese(IV) oxide (MnO_2) (259 mg) in ethyl acetate (5 ml) was

stirred at reflux condition for overnight. After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5/1) to give 117mg of desired compound (45.3%).

MP : 139-140℃.

IR (KBr, cm^{-1}) : 3425, 3143, 3060, 2979, 2947, 2902, 2839, 2235, 1718, 1606.

NMR (DMSO-d_6, δ) : 1.33(3H, t, J=7.1Hz), 3.75(3H, s), 4.34(2H, q, J=7.1Hz), 6.90(2H, dt, J=8.8Hz and 1.9Hz), 7.25(2H, dt, J=8.8Hz and 1.9Hz), 7.52(2H, dt, J=8.5Hz and 1.7Hz), 8.05(2H, dt, J=8.5Hz and 1.7Hz), 8.55(1H, s).

MS : 348 $(M+H)^+$.

Example 24-1

1-(4-Carbamoylphenyl)-4-cyano-2-(4-methoxyphenyl)-1H-imidazole

49mg of desired compound was obtained from 4-cyano-1-(4-ethoxycarbonylphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 23-2 (100mg) in the similar manner that of Example 9-1 (53.5%).

MP : 228-290 ℃.

IR (KBr, cm^{-1}) : 3456, 3396, 3354, 3292, 3172, 3113, 3051, 2970, 2837, 2227, 1682, 1612.

NMR (DMSO-d_6, δ) : 3.75(3H, s), 6.91(2H, d, J=8.8Hz), 7.26(2H, d, J=8.8Hz), 7.46(2H, d, J=8.5Hz), 7.54(1H, s), 7.97(2H, d, J=8.5Hz), 8.11(1H, s), 8.52(1H, s).

MS : 319 $(M+H)^+$.

Example 25-1

4-Cyano-1-(4-cyanophenyl)-2-(4-methoxyphenyl)-1H-imidazole

24mg of desired compound was obtained from 1-(4-carbamoylphenyl)-4-Cyano-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 24-1 (40mg) in the similar manner that of Example 22-1 (63.6%).

MP : 185-186 ℃

IR (KBr, cm^{-1}) : 3419, 3219, 3132, 3091, 3057, 3012, 2968, 2935, 2837, 2229, 1608.

NMR (DMSO-d_6, δ) : 3.76(3H, s), 6.92(2H, d, J=8.8Hz), 7.25(2H, d, J=8.7Hz), 7.59(2H, d, J=8.5Hz), 8.02(2H, d, J=8.5Hz), 8.56(1H, s).

MS : 301 $(M+H)^+$.

Example 26-1

4-Acetyl-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

3N solution of methylmagunesium bromide in diethyl ether (1.17ml) was added to a solution of 4-cyano-1-(4-methoxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole (357mg) in tetrahydrofuran (5ml). After stirring at room temperature for 2hrs, the reaction mixture was poured into hydrochloric acid and extracted with ethyl acetate, washed with water, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (5/1) to give 258mg of desired compound (68.5%).

MP : 116-117℃

IR (KBr, cm^{-1}) : 3431, 3118, 3066, 3008, 2964, 2929, 2837, 1668, 1610.

NMR (DMSO-d_6, δ) : 2.48(3H, s), 3.74(3H, s), 3.80(3H, s), 6.89(2H, d, J=8.6Hz), 7.03(2H, d, J=8.8Hz), 7.26-7.31(4H, m), 8.12(1H, s).

MS : 323 $(M+H)^+$.

Example 27-1

4-Ethoxycarbonyl-4,5-dihydro-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A mixture of N^1-(4-benzyloxyphenyl)-4-methoxybenzamidine (1.25g), ethyl 2-chloroacrylate (0.76g) and N,N-diisopropylethylamine (0.98ml) in tetrahydrofuran (12ml) was stirred at reflux condition for 2hrs. After cooling to room temperature, the reaction mixture was filtered off and the filtrate was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo.

This material was used in the next step without further purification.

Example 27-2

4-Ethoxycarbonyl-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

The residue of Example 27-1 was dissolved in N,N-dimethylformamide (10ml), and manganese(IV) oxide (1.63g) was added to the solution. After stirring at 100℃ for 4hrs, the reaction mixture was cooled to room temperature and poured into water and ethyl acetate. After filtration, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 1.5g of desired compound as an oil (93.1%).

IR (Neat, cm^{-1}) : 3433, 3253, 3224, 3140, 3064, 2966, 2843, 1722, 1712, 1606.

NMR (DMSO-d_6, δ) : 1.29(3H, t, J=7.1Hz), 3.75(3H, s), 4.27(2H, d, J=7.1Hz), 5.15(2H, s), 6.88(2H, dt, J=8.9Hz and 1.9Hz), 7.10(2H, dt, J=8.9Hz and 1.9Hz), 7.24-7.49(9H, m), 8.04(1H, s).

MS : 429 $(M+H)^+$.

Example 28-1

1-(4-Benzyloxyphenyl)-4-formyl-2-(4-methoxyphenyl)-1H-imidazole

0.95N Diisopropylalminiumhydride in toluene (6.49ml) was added dropwise to a solution of 4-ethoxycarbonyl-1-(4-benzyloxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 27-1 (0.88g) in dichloromethane (5ml) under stirring at -78℃, and stirred at -78℃ for 2hrs. The reaction mixture was quenched by sat. ammonium chloride aq., then 1N hydrochloric acid was added and extracted with water. After sodium hydroxide aq. was added, extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was dissolved in N,N-dimethylformamide (10ml), and manganese(IV) oxide (1.79g) was added to the solution. After stirring at 100℃ for 1hr, the reaction mixture was cooled to room temperature and poured into water and ethyl acetate. After filtration, the mixture was extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.77g of desired compound as an oil (97.5%).

IR (Neat, cm^{-1}) : 3440, 3361, 3219, 3124, 3062, 2937, 2837, 2760, 1732, 1684, 1610.

NMR (DMSO-d_6, δ) : 3.75(3H, s), 5.16(2H, s), 6.89(2H, dt, J=8.9Hz and 1.9Hz), 7.12(2H, dt, J=8.9Hz and 2.1Hz), 7.27-7.49(9H, m), 8.28(1H, s), 9.82(1H,s).

MS : 385 $(M+H)^+$.

Example 29-1

1-(4-Benzyloxyphenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole

Diethylaminosulfur trifluoride (0.46 ml) was added to a solution of 1-(4-benzyloxyphenyl)-4-formyl-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 28-1 (0.45g) in dichloromethane (5ml) under stirring at 0℃. After stirring at room temperature for overnight, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.38g of desired compound as an oil (79.9%).

IR (Neat, cm^{-1}) : 3433, 3155, 3113, 3066, 3041, 2964, 2841, 1732, 1610.

NMR (DMSO-d_6, δ) : 3.74(3H, s), 5.15(2H, s), 6.87(2H, d, J=8.9Hz), 7.08(1H, t, J=55.0Hz), 7.10(2H, d, J=8.9Hz), 7.24-7.45(9H, m), 7.73(1H, t, J=2.3Hz).

MS : 407 $(M+H)^+$.

Example 30-1

4-Difluoromethyl-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole

A suspension of 1-(4-benzyloxyphenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 29-1 (0.38g) and dry 20% palladium hydroxide on carbon ($Pd(OH)_2/C$) (100mg) in ethanol (8ml) and cyclohexene (4ml) was stirred at reflux condition for 1hr and cooled to room temperature. After filtration, the reaction mixture was evaporated in vacuo to give 0.3g of desired compound (ca.100%).

MP : 143-145℃

IR (KBr, cm^{-1}) : 3149, 3111, 3003, 2966, 2837, 2804, 2679, 2602, 1610.

NMR (DMSO-d_6, δ) : 3.74(3H, s), 6.80-6.91(4H, m), 6.96(1H, t, J=55.0Hz), 7.14(2H, dt, J=8.7Hz and 1.9Hz), 7.27(2H, dt, J=8.9Hz and 1.9Hz), 7.68(1H, t, J=2.2Hz), 9.90(1H, s).
MS : 317 $(M+H)^+$.

Example 31-1
4-Difluoromethyl-2-(4-methoxyphenyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole

Triethylamine (0.15ml) and trifluoromethanesulfonic anhydride (0.18ml) was added to a solution of 4-difluoromethyl-1-(4-hydroxyphenyl)-2-(4-methoxyphenyl)-1H-imidazole obtained by Example 30-1 (300mg) in chloroform (5ml) under stirring at 0℃. After stirring at 0℃ for 4hrs, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 0.24g of desired compound as an oil (56.4%).

IR (Neat, cm^{-1}) : 3159, 3118, 3078, 3006, 2939, 2848, 1610.
NMR (DMSO-d_6, δ) : 3.74(3H, s), 6.89(2H, dt, J=8.9Hz and 1.9Hz), 7.01(1H, t, J=54.8Hz) 7.23(2H, dt, J=8.9Hz and 2.0Hz), 7.54-7.69(4H, m), 7.92(1H, t, J=2.3Hz).
MS : 449 $(M+H)^+$.

Example 31-2
1-(4-Cyanophenyl)-4-difluoromethyl-2-(4-methoxyphenyl)-1H-imidazole

A suspension of 4-difluoromethyl-2-(4-methoxyphenyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole obtained by Example 31-1 (0.2g), zinc cyanide ($Zn(CN)_2$) (55mg) and

tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) (272mg) in N,N-dimethylformamide (1ml) was stirred at 85℃ for overnight under nitrogen atmosphere then cooled to room temperature. After filtration, the reaction mixture was poured into water and extracted with ethyl acetate, dried over magnesium sulfate and evaporated in vacuo. The residue was purified by silica gel column chromatography eluting with n-hexane/ethyl acetate (1/1) to give 83mg of desired compound (47.7%).

MP : 131-132℃.

IR (KBr, cm^{-1}) : 3222, 3157, 3114, 2966, 2839, 2231, 1610.

NMR (DMSO-d_6, δ) : 3.75(3H, s), 6.91(2H, dt, J=8.9Hz and 1.9Hz), 7.02(1H, t, J=54.8Hz), 7.24(2H, dt, J=8.8Hz and 2.0Hz), 7.55 (2H, dt, J=8.7Hz and 1.7Hz), 7.93(1H, t, J=2.2Hz), 7.95(2H, dt, J=8.5Hz and 2.0Hz).

MS : 326 $(M+H)^+$.

Example 32-1

1-(4-Benzyloxyphenyl)-4,5-dihydro-4-ethoxycarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole

2.67g of desired compound was obtained from a mixture of N^1-(4-benzyloxyphenyl)-2-methoxy-5-amidinopyridine (2.57g) and ethyl 2-chloacrylate (1.56g) in the similar manner that of Example 11-1 (80.3%).

IR (Neat, cm^{-1}) : 3448, 3411, 3378, 3037, 2981, 2949, 2902, 1734, 1608.

NMR (DMSO-d_6, δ) : 1.24(3H, t, J=7.1Hz), 3.83(3H, s), 4.06(2H, d, J=9.9Hz), 4.17(2H, q, J=7.1Hz), 4.81(1H, t, J=9.8Hz), 5.04(2H, s), 6.77(1H, d, J=8.6Hz), 6.93(4H, s), 7.29-7.44(5H, m), 7.68(1H, dd, J=8.6Hz and 2.4Hz), 8.18(1H, d, J=2.4Hz).

MS : 432 $(M+H)^+$.

Example 32-2

1-(4-Benzyloxyphenyl)-4-ethoxycarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole

1.74g of desired compound was obtained from a suspension of 1-(4-benzyloxyphenyl)-4,5-dihydro-4-ethoxycarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Example 32-1 (2.67g) in N,N-dimethylformamide (27ml) in the similar manner that of Example 23-2 (65.5%).

MP : 109-110℃.

IR (KBr, cm^{-1}) : 3433, 3390, 3136, 3070, 2976, 2941, 2841, 1693, 1608.

NMR (DMSO-d_6, δ) : 1.29(3H, t, J=7.1Hz), 3.84(3H, s), 4.28(2H, q, J=7.1Hz), 5.15(2H, s), 6.80(1H, d, J=8.6Hz), 7.12(2H, d, J=8.9Hz), 7.32-7.49(7H, m), 7.65(1H, dd, J=8.6Hz and 2.4Hz), 8.06(1H, d, J=2.4Hz), 8.12(1H, s).

MS : 430 $(M+H)^+$.

Example 33-1

1-(4-Benzyloxyphenyl)-4-formyl-2-(2-methoxy-5-pyridyl)-1H-imidazole

0.83g of desired compound was obtained from 1-(4-benzyloxyphenyl)-4-ethoxycarbonyl-2-(2-methoxy-5-pyridyl)-1H-imidazole (1.46g) in the similar manner that of Example 28-1 (63.3%).

IR (Neat, cm^{-1}) : 3217, 3126, 3059, 2947, 2831, 2760, 1687, 1606.

NMR (DMSO-d_6, δ) : 3.84(3H, s), 5.16(2H, s), 6.82(1H, d, J=8.5Hz), 7.14(2H, dt, J=8.9Hz and 2.0Hz), 7.35-7.50(7H, m), 7.66(1H, dd, J=8.6Hz and 2.5Hz), 8.11(1H, d, 2.3Hz), 8.35(1H, s), 9.84(1H, s).

MS : 386 $(M+H)^+$.

Example 34-1

1-(4-Benzyloxyphenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridyl)-1H-imidazole

0.48g of desired compound was obtained from 1-(4-benzyloxyphenyl)-4-formyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Example 33-1 (0.83g) in the similar manner that of Example 29-1 (54.7%).

IR (Neat, cm^{-1}) : 3429, 3209, 3151, 3064, 3028, 2979, 2949, 2875, 2549, 1734, 1604.

NMR (DMSO-d_6, δ) : 3.84(3H, s), 5.15(2H, s), 6.80(1H, d, J=8.5Hz), 7.00(1H, t, J=54.8Hz), 7.12(2H, d, J=9.0 Hz), 7.27-7.49(7H, m), 7.63(1H, dd, J=8.6Hz and 2.5Hz), 7.81(1H, t, J=2.2Hz), 8.07(1H, d, J=1.8Hz).

MS : 408 $(M+H)^+$.

Example 35-1

4-Difluoromethyl-1-(4-hydoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole

0.48g of desired compound was obtained from 1-(4-benzyloxyphenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Example 34-1 (0.48 g) in the similar manner that of Example 30-1 (ca.100%).

MP : 155-156℃.

IR (KBr, cm^{-1}) : 3012, 2962, 2808, 2681, 2603, 1603.

NMR (DMSO-d_6, δ) : 3.83(3H, s), 6.77-6.86(3H, m), 6.99(1H, t, J=54.9Hz), 7.19(2H, d, J=8.8Hz), 7.63(1H, dd, J=8.7Hz and 2.5Hz), 7.76(1H, t, J=2.2Hz), 8.06(1H, d, J=2.4Hz), 10.06(1H, br).

MS : 318 $(M+H)^+$.

Example 36-1

4-Difluoromethyl-2-(2-methoxy-5-pyridyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole

0.2g of desired compound was obtained from 4-difluoromethyl-1-(4-hydoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Example 35-1 (0.17g) in the similar manner that of Example 31-1(83.1%).

IR (Neat, cm^{-1}) : 3429, 3224, 3165, 3084, 3020, 2958, 2860, 1724, 1664, 1604.

NMR (DMSO-d_6, δ) : 3.84(3H, s), 6.80(2H, d, J=8.4Hz), 7.03(1H, t, J=54.8Hz), 7.56-7.71(4H, m), 7.99(1H, t, J=2.2Hz), 8.09(1H, d, J=2.4Hz).

MS : 450 $(M+H)^+$.

Example 36-2

1-(4-Cyanophenyl)-4-difluoromethyl-2-(2-methoxy-5-pyridyl)-1H-imidazole

62mg of desired compound was obtained from 4-difluoromethyl-2-(2-methoxy-5-pyridyl)-1-(4-trifluoromethanesulfonyloxyphenyl)-1H-imidazole obtained by Example 36-1 (0.2g) in the similar manner that of Example 31-2 (42.7%).

MP : 160-161℃.

IR (KBr, cm^{-1}) : 3219, 3140, 3101, 3051, 3005, 2985, 2954, 2241, 1608.

NMR (DMSO-d_6, δ) : 3.85(3H, s), 6.82(1H, d, J=8.6Hz), 7.04(1H, t, J=54.7Hz), 7.57-7.63(3H, m), 7.99-8.03(3H, m), 8.11(1H, d, J=2.3Hz).

MS : 327 $(M+H)^+$.

Example 37-1

4-Ethoxycarbonyl-4,5-dihydro-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole

5.41g of desired compound was obtained from a mixture of

N^1-(4-methoxyphenyl)-2-methoxy-5-amidinopyridine (5g) and ethyl 2-chloroacrylate (3.92g) in the similar manner that of Example 11-1 (78.3%).

IR (Neat, cm^{-1}) : 3448, 3429, 3411, 3381, 3047, 2981, 2951, 2904, 2841, 1736, 1608.

NMR (DMSO-d_6, δ) : 1.24(3H, t, J=7.1 Hz), 3.73(3H, s), 3.83(3H, s), 4.05(2H, d, J=9.5Hz), 4.17(2H, q, J=7.1Hz), 4.81(1H, t, J=9.5Hz), 6.77(1H, d, J=8.5Hz), 6.79-6.96(4H, m), 7.67(1H, dd, J=8.6Hz and 2.4Hz), 8.17(1H, d, J=2.3Hz).

MS : 356 $(M+H)^+$.

Example 37-2

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole

3.71g of desired compound was obtained from a suspension of 4-ethoxycarbonyl-4,5-dihydro-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Example 37-1 (5.41g) in N,N-dimethylformamide (54ml) in the similar manner that of Example 23-2 (69%).

MP : 135-137 ℃.

IR (KBr, cm^{-1}) : 3413, 3224, 3145, 3070, 2949, 2902, 2837, 1703, 1610.

NMR (DMSO-d_6, δ) : 1.29(3H, t, J=7.1Hz), 3.81(3H, s), 3.83(3H, s), 4.28(2H, q, J=7.1Hz), 6.80(1H, d, J=8.6Hz), 7.04(2H, dt, J=8.9Hz and 2.0Hz), 7.34(2H, dt, J=8.9Hz and 2.2Hz), 7.64(1H, dd, J=8.6Hz and 2.5Hz), 8.06(1H, d, J=2.4Hz), 8.11(1H, s).

MS : 354 $(M+H)^+$.

Example 38-1

4-Formyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole

0.88g of desired compound was obtained from 4-ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Example 37-21 (1.7g) in the similar manner that of Example 28-1 (59.1%).

IR (Neat, cm^{-1}) : 3435, 3367, 3134, 3074, 3006, 2960, 2846, 1682, 1608.

NMR (DMSO-d_6, δ) : 3.81(3H, s), 3.84(3H, s), 6.82(1H, d, J=8.5Hz), 7.06(2H, dt, J=8.9Hz and 1.9Hz), 7.37(2H, dt, J=8.9Hz and 1.9Hz), 7.65(1H, dd, J=8.6Hz and 2.5Hz), 8.11(1H, d, J=2.1Hz), 8.34(1H, s), 9.84(1H, s).

MS : 310 $(M+H)^+$.

Example 39-1

4-Difluoromethyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole

332mg of desired compound was obtained from 4-formyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole obtained by Example 38-1 (0.83g) in the similar manner that of Example 29-1 (36.5%).

MP : 106-107 ℃.

IR (KBr, cm^{-1}) : 3398, 3153, 3114, 2997, 2947, 2844, 1606.

NMR (DMSO-d_6, δ) : 3.81(3H, s), 3.83(3H, s), 6.80(1H, d, J=8.8Hz), 7.00(1H, t, J=54.9Hz), 7.04(2H, dt, J=8.9Hz and 2.1Hz), 7.33(2H, dt, J=8.8Hz and 2.1Hz), 7.63(1H, dd, J=8.6Hz and 2.5Hz), 7.80(1H, t, J=2.3Hz), 8.07(1H, d, J=2.4Hz).

MS : 332 $(M+H)^+$.

Example 40-1

4-Ethoxycarbonyl-1-(4-methoxyphenyl)-2-(2-methoxy-5-pyridyl)-1H-imidazole

1.5g of desired compound was obtained from a suspension of

N^1-(4-methoxyphenyl)-2-methoxy-5-amidinopyridine (1.5g) in 2-propanol (10ml) in the similar manner that of Example 8-1 (72.8%).

In order to illustrate the usefulness of the object compounds (I), the pharmacological test data of the compounds (I) are shown in the following.

[A] ANALGESIC ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Analgesic activity of a single dose of agents in arthritic rats was studied.

Arthritis was induced by injection of 0.5 mg of Mycobacterium tuberculosis (Difco Laboratories, Detroit, Mich.) in 50μl of liquid paraffin into the right hind footpad of Lewis rats aged 7 weeks. Arthritic rats were randomized and grouped (n=10) for drug treatment based on pain threshold of left hind paws and body weight on day 22.

Drugs (Test compounds) were administered and the pain threshold was measured 2hrs after drug administration. The intensity of hyperalgesia was assessed by the method of Randall - Selitto. The mechanical pain threshold of the left hind paw (uninjected hind paw) was determined by compressing the ankle joint with a balance pressure apparatus (Ugo Basile Co.Ltd., Varese, Italy). The threshold pressure of rats squeaking or struggling was expressed in grams. The threshold pressure of rats treated with drugs was compared with that of non-treated rats. A dose showing the ratio of 1.5 is considered to be the effective dose.

(ii) Test Results:

Test compound (Example No.)	Dose (mg/kg)	The coefficient of analgesic
3-2	3.2	>1.5
10-1	3.2	>1.5
22-1	3.2	>1.5
26-1	3.2	>1.5
36-2	3.2	>1.5
39-1	3.2	>1.5

[B] Inhibiting activity against COX-I and COX-II (Whole Blood Assay):

(i) Test Method :

Whole blood assay for COX-I

Fresh blood was collected by syringe without anticoagulants from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500μl aliquots of human whole blood were immediately incubated with 2μl of either dimethyl sulfoxide vehicle or a test compound at final concentrations for 1hr at 37℃ to allow the blood to clot. Appropriate treatments (no incubation) were used as blanks. At the end of the incubation, 5μl of 250mM Indomethacin was added to stop the reaction. The blood was centrifuged at 6000 x g for 5min at 4℃ to obtain serum. A 100 μl aliquot of serum was mixed with 400μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4℃ and was assayed for TXB_2 using an enzyme immunoassay kit according to the manufacturer's procedure. For a test compound, the results were expressed as percent inhibition of thromboxane B_2(TXB_2) production relative to control incubations

containing dimethyl sulfoxide vehicle.

The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

Whole blood assay for COX-II

Fresh blood was collected in heparinized tubes by syringe from volunteers with consent. The subjects had no apparent inflammatory conditions and had not taken any medication for at least 7 days prior to blood collection.

500 μl aliquots of human whole blood were incubated with either 2 μl dimethyl sulfoxide vehicle or 2 μl of a test compound at final concentrations for 15 min at 37℃. This was followed by incubation of the blood with 10 μl of 5mg/ml lipopolysaccharide for 24hrs at 37℃ for induction of COX-II. Appropriate PBS treatments (no LPS) were used as blanks. At the end of the incubation, the blood was centrifuged at 6000 x g for 5 min at 4 ℃ to obtain plasma. A 100 μl aliquot of plasma was mixed with 400 μl methanol for protein precipitation. The supernatant was obtained by centrifuging at 6000 x g for 5min at 4℃ and was assayed for prostaglandin E_2 (PGE_2) using a radioimmunoassay kit after conversion of PGE_2 to its methyl oximate derivative according to the manufacturer's procedure.

For a test compound, the results were expressed as percent inhibition of PGE_2 production relative to control incubations containing dimethyl sulfoxide vehicle. The data were analyzed by that a test compound at the indicated concentrations was changed log value and was applied simple linear regression. IC_{50} value was calculated by least squares method.

(ii) Test Results:

Test Compound (Example No.)	COX-I IC50 (μM)	COX-II IC50 (μM)
1-2	< 0.01	$\geqq 0.1$
3-2	< 0.01	$\geqq 0.1$
4-2	< 0.01	$\geqq 0.1$
7-2	< 0.01	$\geqq 0.1$
10-1	< 0.01	$\geqq 0.1$
15-1	< 0.01	$\geqq 0.1$
18-1	< 0.01	$\geqq 0.1$
19-1	< 0.01	$\geqq 0.1$
22-1	< 0.01	$\geqq 0.1$
31-2	< 0.01	$\geqq 0.1$
36-2	< 0.01	$\geqq 0.1$
39-1	< 0.01	$\geqq 0.1$

It appeared, from the above-mentioned Test Results, that the compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against COX, particularly a selective inhibiting activity against COX-I.

Additionally, it was further confirmed that the compounds (I) of the present invention lack undesired side-effects of non-selective NSAIDs, such as gastrointestinal disorders, bleeding, renal toxicity, cardiovascular affection, etc. So compound (I) or a salt thereof is expected to be useful as medicament.

The object compound (I) or pharmaceutically acceptable salts thereof of this invention possesses COX inhibiting activity and possesses strong anti-inflammatory, antipyretic, analgesic, antithrombotic, anti-cancer activities, and so on.

The object compound (I) and pharmaceutically acceptable salt thereof, therefore, are useful for treating and/or preventing

COX mediated diseases, inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals by using administered systemically or topically.

More particularly, the object compound (I) and pharmaceutically acceptable salts thereof are useful for treating and/or preventing inflammation and acute or chronic pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodose, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimers disease, or the like.

Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

And compound (I) or a salt thereof is expected to be useful as analgesic agent, which is usable for treating or preventing pains caused by or associated with acute or chronic inflammations, for example rheumatoid arthritis, osteoarthritis, lumbar

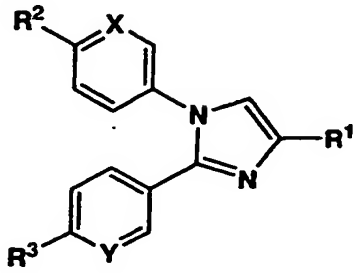
rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury.

Although the present invention has been fully described by way of example, it is to be understood that various changes and modifications will be apparent to those skilled in the art. Therefore, unless otherwise such changes and modifications depart from the scope of the present invention hereinafter defined, they should be construed as being included therein.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of the formula (I):



(I)

wherein

R^1 is lower alkyl, halogen-substituted lower alkyl, hydroxy-substituted lower alkyl, cycloalkyl, carbamoyl, N-(lower alkyl)carbamoyl, N,N-di(lower alkyl)carbamoyl, formyl, lower alkanoyl, carboxy, (lower alkoxy)carbonyl, or cyano;

R^2 is halogen, cyano, hydroxy, lower alkoxy, aryl(lower alkyl)oxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is lower alkoxy, hydroxy, amino, (lower alkyl)amino, or di(lower alkyl)amino;

X and Y are each CH or N;

or pharmaceutically acceptable salts thereof.

2. A compound according to Claim 1, wherein

R^1 is lower alkyl, halogen-substituted lower alkyl, cycloalkyl, N,N-di(lower alkyl)carbamoyl, lower alkanoyl, or cyano;

R^2 is halogen, cyano, hydroxy, or lower alkoxy;

R^3 is lower alkoxy;

X and Y are each CH, X is N and Y is CH, or X is CH and Y is N;

or pharmaceutically acceptable salts thereof.

3. A medicament comprising a compound of Claim 1 or 2 as an active

ingredient.

4. A pharmaceutical composition comprising a compound of Claim 1 or 2 as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

5. A method for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegerative diseases which comprises administering an effective amount of the compound of Claim 1 or 2 to human beings or animals.

6. The compound of Claim 1 or 2 for use in the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegerative diseases in human beings or animals.

7. Use of the compound of Claim 1 or 2 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegerative diseases in human beings or animals.

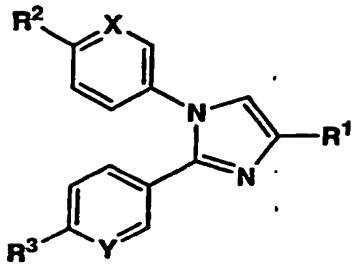
8. The analgesic agent comprising the compound of Claim 1 or 2, which is usable for treating and/or preventing pains caused by or associated with acute or chronic inflammations.

9. The analgesic agent of Claim 8, which is usable for treating or preventing pains caused by or associated with rheumatoid arthritis, osteoarthritis, lumbar rheumatism, rheumatoid spondylitis, gouty arthritis, juvenile arthritis; lumbago; cervico-omo-brachial syndrome; scapulohumeral periarthritis; pain and tumescence after operation or injury.

DATED this 8th day of May, 2003
Fujisawa Pharmaceutical Co., Ltd.
By DAVIES COLLISON CAVE
Patent Attorneys for the Applicant

A B S T R A C T

A compound of the formula (I):



(I)

wherein

R^1 is lower alkyl, etc;

R^2 is halogen, cyano, hydroxy, lower alkoxy, aryl(lower alkyl)oxy, (lower alkoxy)carbonyl, or carbamoyl;

R^3 is lower alkoxy, hydroxy, amino, (lower alkyl)amino, or di(lower alkyl)amino;

X and Y are each CH or N;

or pharmaceutically acceptable salts thereof, which are useful as a medicament.